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Preoperative Radiotherapy and Surgery for Advanced Thymoma With Invasion to the Great Vessels

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From 1983 to 1994, 12 advanced thymomas with invastion to the great vessels were initially treated by irradiation (mean dose, 18.3 Gy) and subsequent surgical resection. In nine patients, complete resection was possible by concomitant resection of the surrounding tissues, mainly pericardium and/or brachiocephalic vein. Histologically, all tumors showed prominent fibrosis. Ten patients also received postoperative radiotherapy (mean dose, 42.3 Gy). Tumor-related deaths occurred in only two patients; one who did not receive postoperative irradiation 21 months and one who had viable cells at the surgical margin 10 months after operation. However, there were also 2 patients who died of respiratory failure due to operation and/or irradiation, one 45 days and the other 7 years after the treatment. Preoperative radiotherapy could facilitate complete resection of the advanced thymomas. The prognosis of the patients treated with preoperative radiotherapy seemed fair if followed by adequate resection and subsequent irradiation.

KEY WORDS: **invasive thymoma, preoperative radiotherapy, surgery**

INTRODUCTION

Invasive thymomas have various degrees and modes of invasiveness, ranging from only capsular invasion to extensive infiltration into the adjacent structures. However, extension of the tumor is mostly limited within the local sites, even if it is advanced [1–3]. Therefore, local control of the tumor may be the most appropriate strategy in treatment of invasive thymoma.

Invasive thymomas usually require concomitant resection of surrounding tissue [4,5]. In many cases, however, epecially for patients with tumor invasion to the intrathoracic great vessels, surgery fails to remove the total tumor mass. Therefore, the radiosensitivity of the invasive tumor indicates adjuvant radiotherapy to surgery for the completion of its local control [6–8]. Radiotherapy is more commonly administered postoperatively than preoperatively.

Resectability is closely related to the prognosis of locally invasive thymoma [9,10]. This means that if preoperative therapy can reduce the tumor mass, it may play an important role in the surgical treatment of the invasive tumor. However, the efficacy of preoperative adjuvant radiotherapy and chemotherapy for advanced invasive thymoma has been yet undetermined. Herein, our experience with surgical treatment with preoperative radiotherapy for large invasive tumors with infiltration into the great vessels is described.

PATIENTS AND METHODS

From 1983 to 1994, 25 patients with invasive thymoma received surgical resection and irradiation at our hospital. During this period, two thymic cancers, one thymic carcinoid, and four thymic malignant lymphomas were also experienced. These thymic tumors were excluded in the

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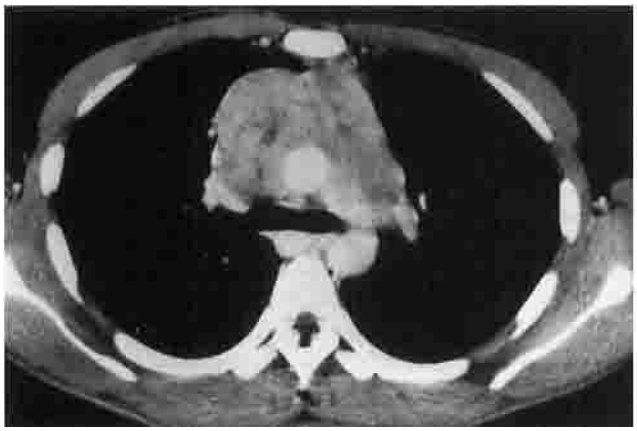

Fig. 1. Chest CT findings of invasive thymoma in patient No. 12. Tumor involves the superior vena cava (SVC), aorta, and left pulmonary artery. Note that the SVC is almost occluded.

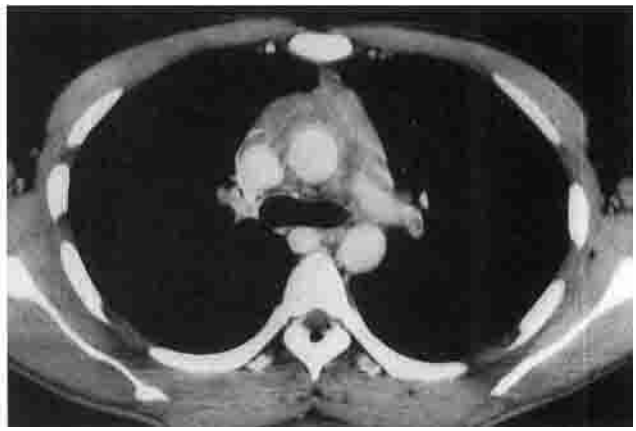

Fig. 2. Chest CT findings at the same level of Figure 1 in the same patient after preoperative irradiation. Tumor prominently shrank, and the SVC is recanalized.

study. Our criterion for preoperative radiotherapy for invasive thymoma was the apparent involvement of the tumor in the surrounding great vessels, i.e., the superior vena cava (SVC), aorta and/or pulmonary artery, in chest computed tomography (CT) scans (Fig. 1)—a condition that often leads to incomplete resection of the tumor. According to this criterion, 12 patients with large invasive thymoma were initially treated with irradiation. In all patients who received preoperative radiotherapy, histological diagnosis was obtained by transcutaneal needle biopsy from the tumor before treatment. First, the characteristics of all the patients with invasive thymoma were demonstrated. Next, the results of the treatment of patients with locally advanced tumors infiltrating into the great vessels were analyzed.

The degree of invasiveness was evaluated by Masaoka's classification: stage I, encapsulated tumors without microscopic capsular invasion; stage II, tumors with macroscopic invasion into the mediastinal fatty tissue or mediastinal pleura, or microscopic invasion to the capsule; stage III, tumors with macroscopic invasion to the surrounding organs, i.e., the pericardium, great vessels or lung; stage IVa, tumors with pleural or pericardial dissemination; and stage IVb, tumors with lymphogenous or hematogenous metastasis or both [1].

Preoperatively, patients with tumor invasion to the great vessels in chest CT received a total of dose of 12–21-Gy irradiation to the tumor in 2 or 3 weeks with 5 fractions per week, using two opposing anteroposterior beams. Response was precisely evaluated by chest CT scan (Fig. 2): partial response (PR), a decrease of 30% or more in the maximal diameter of the tumor; no change (NC), a decrease less than 30% in maximal tumor size.

Surgical resection was performed 10–20 days after radiotherapy. All patients underwent median sternotomy. Complete resection means total thymothymectomy and resection of involved surrounding structures with postoperative histological confirmation of the absence of viable tumor cells at surgical margin. All other types of operation are called incomplete resection, i.e., subtotal resection or tumor debulking. Postoperative irradiation was started from 3 weeks after the operation in most patients.

Biopsied or resected specimens were fixed in 10% formaldehyde and embedded in paraffin for histological study. Three- to 4-μm-thick sections were stained with hematoxylin and eosin (H&E), periodic acid-Schiff, and Masson's trichrome. Additionally, immunohistochemical analysis using epithelial membrane antigen (Dako, Santa Barbara, CA) and cytokeratin (Dako) was performed. Histologically, the tumors were classified into three types based on the degree of lymphocytic infiltration into the tumor: predominantly lymphocytic type, mixed lymphoepithelial type, and predominantly epithelial type.

Median follow-up time was 77.6 months (12–140 months). The follow-up time was less than 5 years (12–52 months) for four surviving patients.

Statistical analysis by chi-square test was used to compare the two groups. Survival rate was calculated by the Kaplan–Meier method and statistically analyzed by the generalized Wilcoxon test.

RESULTS

Preoperative irradiation was easily and safely performed in all patients. Patient characteristics are summarized in Table I based on comparison with patients who did not receive preoperative radiotherapy. Patients who received preoperative irradiation were significantly younger than those who did not ($P < 0.01$). Tumors that underwent preoperative radiation therapy were significantly larger (12.7 cm in mean maximal diameter) than those that did not ($P < 0.002$). All of the 4 patients with myasthenia gravis were in the group not receiving preop-

TABLE I. Patient Characteristics of Resected Invasive Thymomas*

	With preoperative radiotherapy	Without preoperative radiotherapy	Total
No. of patients (M/F)	12 (8/4)	13 (8/5)	25 (16/9)
Average age (years)	35.7 (19–67)	54.0 (41–70)	45.2
Tumor size (cm)	12.7 (8–18.5)	6.5 (4–10)	9.5
Patients with MG	0	4	4
Histological subtype			
Lymphocytic	2	3	5
Epithelial	5	4	9
Mixed	5	6	11
Tumor stage			
II	0	10	10
III	11	2	13
IVa	0	1	1
IVb	1	0	1

*M, male; F, female; MG, myasthenia gravis.

TABLE II. Results of Surgical Treatment for Invasive Thymoma

	With preoperative radiotherapy	Without preoperative radiotherapy	Total
Resectability rate (%)	75	76.9	76
Overall survival (%)[a]			
5-year	72.2	100	87.3
10-year	48.2	100	74.8

[a]There is a significant difference in survival rate between the groups ($P = 0.032$).

erative radiotherapy. Stage III disease was found in all of the patients who received preoperative radiotherapy, except for one, who was found to have stage IVa disease with only a minimal mediastinal lymph node metastasis, by histological examination of the resected specimen.

The results of surgical treatment for invasive thymoma are summarized in Table II. The rate of complete resection in the group of patients who received preoperative radiotherapy was high (75%) in spite of the marked invasiveness of the tumors. However, the overall survival rate of the group was clearly lower than that of the group that did not receive it ($P = 0.032$).

The clinical and histological data of patients with invasive thymoma treated with preoperative radiotherapy are shown in Table IIIA and B. Except for one patient who showed no change, all patients showed good response to preoperative radiotherapy (mean dose, 18.3 Gy) in CT scan. In all patients, combined resections of surrounding structures were required. Partial resection of the involved pericardium and resection of the brachiocephalic vien were performed in all patients but one, respectively; lung resection was performed in 10 (partial in 9 and lobectomy in one); phrenic nerve resection in 5 (bilateral in one), but SVC resection followed by reconstruction with an artifical graft in only 3. Moreover, tumor debulking was performed in only one patient. Histological examination revealed prominent fibrosis of the tumor in all of the patients, including the one that showed no change in chest CT, but in one patient many visible tumor cells partially remained at the surgical margin of the resected fibrosing tumor.

Postoperative irradiation (mean dose, 42.3 Gy) was also performed in all but two patients; one with postoperative pulmonary insufficiency resulting in hosptial death 45 days after operation, and the other diagnosed with active pulmonary tuberculosis after the operation (Table IIIB). The only acute complications of radiotherapy observed were slight dermatitis and transient mucositis. However, radiation fibrosis of the lung appeared in 3 patients after the radiation therapy.

The overall 5-year and 10-year survival rates were 72.2% and 48.2%, respectively. Operation-associated death occurred in one patient, who died 45 days after operation, as mentioned above. One patient who received bilateral phrenic nerve resection and a high dose of postoperative radiotherapy experienced late death 7 years after operation due to chronic respiratory failure (Table IIIB). Tumor recurrence was seen in only two patients. The first of these two patients did not receive postoperative radiotherapy because of active pulmonary tuberculosis, as mentioned before, and died of local recurrence and distant metastasis 21 months after operation. The other had residual tumor cells at the surgical margin, and died of massive local recurrence 10 months after operation.

TABLE IIIA. Clinical and Histological Data of Patients With Advanced Invasive Thymomas Who Received Preoperative Radiotherapy*

Patient no.	Age	Sex	Tumor size (cm)	Biopsy diagnosis (subtype)	Preoperative radiotherapy (Gy)	Response	Operation
1	24	M	17	Mixed	18	PR	Complete
2	19	M	11	Epithelial	12	PR	Complete
3	32	F	18.5	Epithelial	18	NC	Incomplete
4	21	F	8.5	Lymphocytic	20	PR	Complete
5	29	M	12	Mixed	18	PR	Incomplete
6	33	M	17.5	Epithelial	21	PR	Complete
7	53	F	14.5	Epithelial	19	PR	Incomplete
8	67	F	11	Mixed	18	PR	Complete
9	26	M	13.5	Epithelial	18	PR	Complete
10	46	M	8	Mixed	20	PR	Complete
11	59	M	11	Lymphocytic	20	PR	Complete
12	19	M	10	Mixed	20	PR	Complete

*M, male; F, female; CR, complete response; PR, partial response; NC, no change.

TABLE IIIB. Clinical and Histological Data of Patients With Advanced Invasive Thymomas Who Received Preoperative Radiotherapy*

Patient no.	Combined resection	Tumor histology	Tumor stage	Postoperative radiotherapy (Gy)	Outcome (mo)
1	PR, lt BV, lt PN	Fibrosis	III	38	Alive (140)
2	PR, lt BV, rt L, SVC	Fibrosis	III	40	Alive (131)
3	PR, bi PN, lt L	Fibrosis	III	67	Died (RF, 95)
4	PR, rt BV, rt L	Fibrosis	III	31	Alive (71)
5	Lt BV, lt L	Fibrosis	III	46	Alive (63)
6	PR, rt BV, rt L	Fibrosis (tuberculosis)	III	(−)	Died (RC, MT, 21)
7	PR, lt BV, lt PN	Fibrosis (viable cells)	III	43	Died (RC, 10)
8	PR, lt BV, rt PN, rt L,[a] SVC	Fibrosis	IVb	(−)	Died (RF, 2)
9	PR, lt BV, lt L, lt PN	Fibrosis	III	31	Alive (52)
10	PR, lt BV, lt L	Fibrosis	III	45	Alive (15)
12	PR, bi BV, lt L, SVC	Fibrosis	III	40	Alive (12)

*PR, pericardium; PN, phrenic nerve; BV, brachiocephalic vein; L, lung; SVC, superior vena cava; lt, left; rt, right; bi, bilateral; RF, respiratory failure; RC, recurrence; MT, metastasis.
[a]Right upper lobectomy.
From Verley and Hollmann [2].

Therefore, 5-year and 10-year survival rates based on the tumor death were the same, at 80.8% (Fig. 3).

DISCUSSION

Most encapsulated thymomas can be cured by surgical resection alone. On the other hand, invasive thymomas have a possibility of relapse after surgical resection, even if postoperative radiotherapy has been added [11]. Tumors recur more frequently in stage III thymoma, which involves macroscopic invasion into the surrounding tissues, than in stage II disease, which involves only minimal invasion. However, even for stage III tumors, it is true that a complete resection leads to more favorable prognosis [12,13]. Nevertheless, since the degree of invasiveness of the stage III tumors is so varied, it is difficult to draw any conclusions on the treatment results for the total series of state III tumors.

Since complete resection of the tumors with invasion to the great vessels can usually only be performed with very difficulty, tumor invasion to them in chest CT is an especially ominous sign. Data regarding treatment results for locally advanced thymoma with invasion into the great vessels are very scarce. Shimizu and co-workers [5] reported that surgical resection with vascular reconstruction improved the prognosis of patients with invasive thymoma, but 6 out of 14 patients (43%) with the invasive tumor died of the disease within 3 years after operation in their series. Rea and associates [14] showed that 3 of

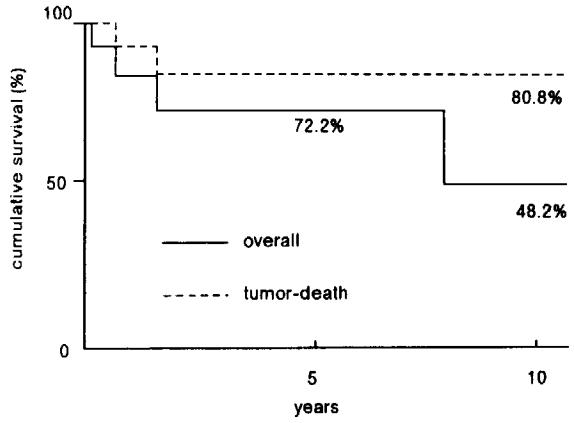

Fig. 3. Survival curves of patients with invasive thymoma treated with preoperative radiotherapy and subsequent surgery.

10 patients (30%) with vascular involvement of invasive thymoma died of the tumor within 21 months after neoadjuvant chemotherapy followed by surgical resection. Furthermore, in their cases, only one patient survived more than 5 years after treatment.

Formerly, Rosai and Levine [15] insisted that preoperative irradiation did not improve the resectability of invasive thymoma at all. Recently, on the contrary, the administration of neoadjuvant therapy, primarily using general chemotherapy, to reduce the size of tumor mass of locally invasive malignancies, has resulted in an increase of the resectability rate of the tumors [14,16]. However, general chemotherapy might be most justifiable in the presence of intrathoracic or extrathoracic dissemination.

Many investigators have reported that radiotherapy is an effective procedure for the local control of invasive thymomas [7–13]. Ohara and associates [17] showed that preoperative radiotherapy, with a total dose of 12–20 Gy, facilitated complete resection of invasive thymoma by reducing tumor mass. In the treatment of advanced invasive thymoma with vascular involvement, local control of the tumor is also considered to have the highest priority, since patients with advanced disease do not always demonstrate any distant metastases [1,2,15]. Therefore, we chose radiotherapy rather than general chemotherapy, as a preoperative treatment modality for locally advanced thymomas.

Preoperative radiotherapy, with a total tumor dose of about 20 Gy, was easily and safely completed within 2 or 3 weeks for all our patients. In this respect, radiotherapy is superior to chemotherapy, which is associated with many unpleasant complications. Moreover, neoadjuvant radiotherapy permitted complete resection of large tumor (12.7 cm in mean maximal primary size) in 9 of 12 patients (75%) undergoing combined resection, primarily the pericardium, the brachiocephalic vein, and the lung. In addition, SVC resection was needed in only three patients because of prominent fibrosis and shrinkage of the tumor.

Since, preoperative radiotherapy results in tumor fibrosis, histological diagnosis of thymoma is very important in preoperative treatment for the advanced tumour. Transcutaneal needle biopsy is beneficial in diagnosing large tumors, which are always located in the anterior mediastinum, widely attaching to the anterior chest wall.

Two of our patients died of pulmonary insufficiency due to treatment; one died of postoperative pulmonary disorder caused by massive resection of surrounding tissues, and the other died of chronic respiratory failure caused by resection of bilateral phrenic nerves and severe radiation fibrosis of the residual lung. This indicates that both aggressive surgery and intensive radiotherapy have the potential to cause severe pulmonary disturbance.

In surgical treatment, combined resection should therefore, be as limited as possible. In particular, caution against phrenic nerve injury and impairment of lung function can be crucial at operation. Moreover, irradiation with a total dose of more than 60 Gy should be avoided due to the increased risk of radiation-associated injuries, as noted by Ciernik and colleagues [12]. Since preoperative irradiation with a dose of 20 Gy could yield prominent fibrosis of the large tumors in all patients we have treated, postoperative radiotherapy at a dose of 40 Gy (total dose of 60 Gy) might be appropriate. However, if any dissemination or metastasis is detected at operation or by postoperative pathological examination, postoperative chemotherapy must be regarded as essential [18].

Although there are still four patients who were followed up for less than 5 years after operation in our series of patients with far-advanced invasive thymomas, the 80.8% 5-year survival rate based on tumor deaths seemed very high. This means, as Shamji et al. [19] had speculated, that preoperative radiotherapy for advanced invasive thymoma might complete local control of the tumor by reducing tumor bulk and preventing "transpleural metastatic seeding at the time of operation." Our data are also insufficient to conclude definitive efficacy of the treatment. However, we believe that preoperative radiotherapy is a simple and effective method of reducing the front areas of tumor invasion and tumor size and that this results in an increase of the resectability of large invasive thymomas. Finally, the prognosis of those patients treated with preoperative radiotherapy may be improved by adequate subsequent treatment.

CONCLUSIONS

Preoperative radiotherapy (mean dose, 18.3 Gy) could facilitate complete resection of the advanced thymomas with invasion to the great vessels. The prognosis of those patients treated with preoperative radiotherapy seemed to be fair if followed by adequate resection and subsequent irradiation (mean dose, 42.3 Gy).

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